PCN81

COST-EFFECTIVENESS OF DABRAFENIB AND TRAMETINIB COMPARED TO PEMBROLIZUMAB AS ADJUVANT TREATMENT OF STAGE III HIGH-RISK BRAF V600E MUTATION-POSITIVE MELANOMA AFTER SURGICAL RESECTION: A BRAZILIAN PRIVATE PAYER PERSPECTIVE

Buehler AM[1], Kim HSJ[1], Fahham L[2], Castilho G[1]

1. Novartis SA; 2. Sense Company

INTRODUCTION Melanoma is a type of cancer originated from the melanocytes – cells responsible for melanin production-, located mostly on the skin[1]. Even though melanoma is the least common skin cancer, it is the most dangerous form due to high potential of spreading towards a metastasis to other parts of the body[2].

In Brazil, the incidence rate is around 3 new cases per 100.000 habitants[3].

Chances of cure are higher when melanoma is early detected[4], and for this reason, the early diagnosis - including the disease stage and presence of mutation - is of major importance for definition of prognosis and choice of best therapeutic approach[4,5,6].

Mutation is a relevant aspect to be considered since different genetic mutations impact the cellular signaling pathways of the disease pathophysiology[7]. BRAF gene mutation is the most common one (40% to 60% of all cases)[8,9].

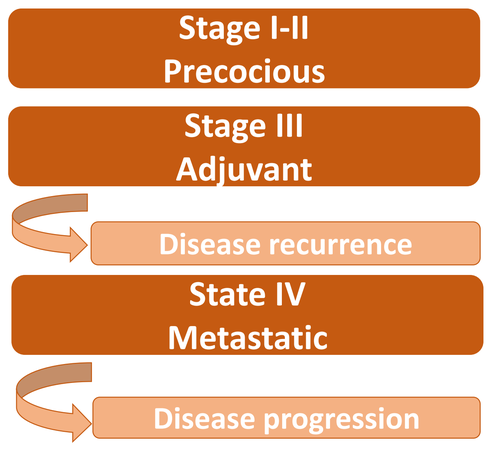

Figure 1. Melanoma Stages.

The mutated BRAF is the only biomarker to predict the therapeutic response in advanced melanoma, and the mechanism of targeted therapies is one of the option for treatment to this population of patients[9,10].

Some therapeutic options have arisen for patients with adjuvant melanoma stage III, after surgical resection, including the target therapy of dabrafenib in combination with trametinib[10,11] and immune checkpoint inhibitors, such as pembrolizumab or nivolumab.

OBJECTIVE The objective of the present study was to evaluate the cost-effectiveness of dabrafenib combined to trametinib in comparison to pembrolizumab in the treatment of patients with stage III high-risk BRAF V600E positive melanoma after surgical resection considering the perspective of the Brazilian Private Healthcare System (BPHS).

METHODS A non-homogeneous semi-Markovian model was developed to estimate the outcomes (Quality-adjusted Life Years –QALYs- and Life years -LYs) and treatment costs under the perspective of the BPHS. The studied population considered adult patients with stage III high-risk BRAF V600E positive melanoma after surgical resection. Half-cycle corrections and 5% discount rate were applied. The adopted horizon of time was 50 years, with semiannual cycles (6 months).

In the model, the patients could transit from one health state to another as demonstrated in Figure 2. Patients entered the model in the Progression-free survival (PFS) state and moved to other 4 states based on recurrence, which may be (1) locoregional or distant [(2) first-line and (3) second-line distant recurrences, and (4) death (representing the absorbing state).

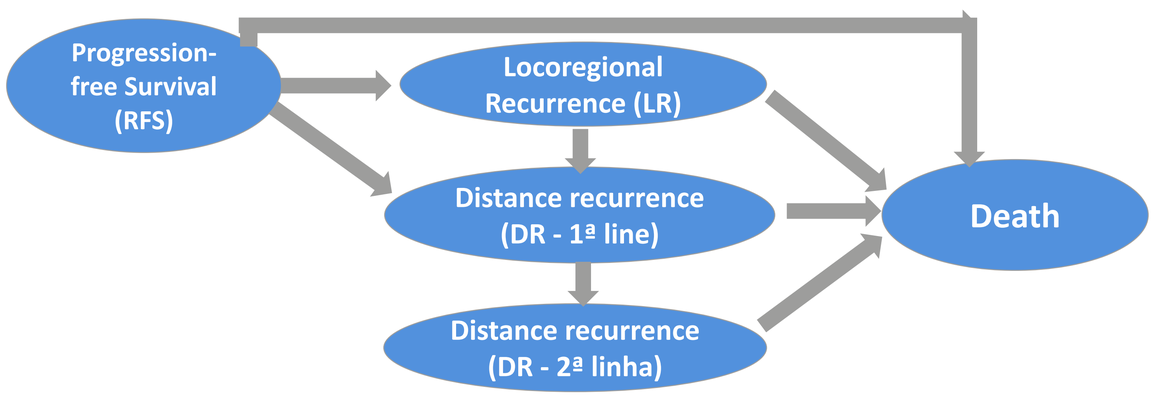

Figure 2. Health states of the model.

The transition probabilities from dabrafenib + trametinib were based on data from the COMBI-AD study[14] and the effects of pembrolizumab were modelled based on PFS hazard ratios (HR) from a network meta-analysis that used watch and wait as a common comparator (HR: 0.57, CI 95%: 0.43-0.75). With the purpose to adequate the outcomes to the horizon of time, the parametric survival distributions were defined based on the Bayesian Information Criteria (BIC) and clinical plausibility (Table 1). For the other health states, the model assumed the same estimates for both treatments.

Table 1. Parametric distribution of each evaluated outcome.

Outcome	Best fit distribution
RFS	Log-logistic unrestricted mixture cure model
RFS after Locoregional Recurrence	Log-logistic unrestricted mixture cure model
Second line treatment progression or death after distance recurrence	Generalized F distribution
Overall survival (OS) for patients receiving second-line treatment	Lognormal

The treatment discontinuation rate and adverse events incidence were based on COMBI-AD[12] study. Also, the utility data were obtained from the COMBI-AD study[13] and based on the EQ-5D-3L questionnaires. To derive HSU for the comparator, disutility upon experiencing adverse events were applied. All utilities were defined by each health state as described in Table 2.

Table 2. Utility data.

Health state	*Utility*
RFS	0.87
LR	0.84
RD first-line (1L)	0.73
RD second-line (2L)	0.66

Direct costs included costs related to drug acquisition, BRAF V600 mutation test, drug administration, disease monitoring, subsequent metastatic-treatment lines, surgery, end-of-life care and management of adverse events.

All drug prices were obtained from official list price CMED (March/2019)[14] (Table 3) and the costs of treatment were calculated based on each drug's label dosage[11,12]. Other costs were estimated considering physician's opinion on resource usage and the Brazilian Hierarchical Classification of Medical Procedures (CBHPM) list[14]. The subsequent metastatic-treatment lines costs represented an average of related therapeutic options after disease progression, including target therapies, immunotherapies and chemotherapy.

Table 3. Drug presentations and prices.

Drug	Presentation	Price	Cost per mg
Dabrafenib	75 mg x 120 capsules	USD 7,993.28	USD 7.69
Trametinib	3 mg x 30 tablets	USD 4,594.78	USD 76.58
Pembrolizumab	100 mg/4mL injection soluction	USD 3,654.1	USD 36.54

The Incremental Cost-Effectiveness Ratio (ICER) per QALY and LY saved was provided for the comparison. Uncertainty of the parameters and robustness of the results were evaluated using deterministic and probabilistic sensitivity analyses.

RESULTS The combination of dabrafenib and trametinib showed to be a dominant alternative in comparison to pembrolizumab, with an incremental gain in effectiveness of 0.18 in QALY and 0.20 in LY and a saving of USD 20,180 (Table 4). The economic savings also reflected the differences in costs related to treatment after 1L and 2L distant relapses.

Table 4. Cost-effectiveness analysis results.

Drugs	Total cost	LY	QALY
Dabrafenib + Trametinib	USD 215,346	10.44	8.37
Pembrolizumab	USD 217,258	10.24	8.19
Incremental	-USD 1,912	0,20	0.18

The results of the sensitivity analyses showed robustness of the model, with the main uncertain parameters represented by relative dose intensity and drug costs. The probabilistic sensitivity analysis showed most of simulations (55.6%) resulted in dabrafenib + trametinib being dominant when compared to pembrolizumab.

A probability of 54% of patients never experiencing a relapse was estimated by the model of cure for PFS.

CONCLUSION In the context of BPHS, the target therapy is a cost-saving alternative in comparison to pembrolizumab in the treatment of adjuvant stage III high-risk BRAF V600E positive melanoma after surgical resection.

1USD = 3.97 BRL (May/2019)

References: 1. Ministério da Saúde . Instituto Nacional de Câncer José Alencar Gomes da S. Tipos de Câncer: Pele - Melanoma. 2016. **2.** Bucheit AD,; **6.** Sociedade Brasileira de Oncologia C. Manual de Condutas 20172017. **7.** Miller AJ, Mihm MC, Jr. Melanoma. N Eng J Med 2006;355:51-6Davies MA. Emerging insights into resistance to BRAF inhibitors in melanoma. Biochemical Pharmacology 2014;87:381-9; **3.** Ministério da Saúde . Instituto Nacional de Câncer José Alencar Gomes da S. Estimativa 2018: incidência de câncer no Brasil. Rio de Janeiro, 2018; **4.** Ministério da Saúde. Secretaria de Atenção à S. Protocolos clínicos e diretrizes terapêuticas em oncologia. Brasília, 2014; **5.** Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: a cancer journal for clinicians 2017;67:472-925; **6.** Shtivelman E, Davies MA, Hwu P, et al. Pathways and therapeutic targets in melanoma. Oncotarget 2014;5:1701-52; **7.** Bruno W, Martinuzzi C, Andreotti V, et al. Heterogeneity and frequency of BRAF mutations in primary melanoma: Comparison between molecular methods and immunohistochemistry. Oncotarget 2017;8:8069-82. **8.** Thomas NE, Edmiston SN, Alexander A, et al. Association Between NRAS and BRAF Mutational Status and Melanoma-Specific Survival Among Patients With Higher-Risk Primary Melanoma. JAMA oncology 2015;1:359-68; **9.** Chang SB, Askew RL, Xing Y, et al. Prospective assessment of postoperative complications and associated costs following inguinal lymph node dissection (ILND) in melanoma patients. Annals of surgical oncology 2010;17:2764-72. **10**. Novartis Biociências SA. Tafinlar (mesilato de dabrafenibe) [Bula]. 2018.; **11.** MSD. Keytruda (pembrolizumabe) [Bula]. 2018**; 12.** Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF -Mutated Melanoma. New England Journal of Medicine 2017;377:1813-23;; 2018.; **13.** Ministério da Saúde. Agência Nacional de Vigilância S. Lista A de medicamentos de referência. Brasília: ANVISA; **14.** (AMB). CBHPM-2017/2018: Classificação Brasileira Hierarquizada de Procedimentos Médicos. 2018.